

REMARKS

The Applicants thank the Examiner for identifying the typographical error in claim 1. In response to the Examiner's objection to claim 1, the word "and" in line 3 has been corrected to read "an". Claim 1 also has been amended to incorporate the limitations of cancelled claim 10.

A copy of all pending claims marked up to show amendments in the Response may be found attached as Appendix A.

Response to Rejection of Claims 1, 2, 7, 8 and 12 under 35 U.S.C. § 102(b)

The Examiner has rejected claims 1, 2, 7, 8 and 12 under 35 U.S.C. § 102(b) as anticipated by Tsuji et al (U.S. Patent No. 5,202,117) in view of Michaelis et al. (U.S. Patent No. 5,919,757). Applicants respectfully traverse this rejection.

Tsuji et al describe a method for the dissolution of thrombi by providing a G-CSF-containing composition. The composition described in Example 2 has a pH of 7. Claim 1 of the present invention has been amended to include a pH range of 6-6.8. Thus, Tsuji et al. no longer anticipates any claim of the present application, and Applicants believe the claims are in condition of allowance.

Response to Rejections under 35 U.S.C. § 103

Claims 3-5, 10, and 11. The Examiner has rejected claims 3-5, 10, and 11 under 35 U.S.C. § 103 as obvious over Tsuji et al (U.S. Patent No. 5,202,117) in view of Michaelis et al. (U.S. Patent No. 5,919,757). Applicants respectfully traverse this rejection. The Examiner does not state how Tsuji et al. and Michaelis et al. would have led, or suggested to, one skilled in the art to choose the compositions claimed in the present application, other than through hindsight, to effect a stable hG-CFS protein formulation.

Tsuji et al. relates to a method of thrombi control and is completely silent as to the stability of the composition. Michaelis et al merely disclose that recombinant hG-CFS made in CHO cells is glycosylated, and likewise is silent as to the stability of the protein. There is no teaching in either reference that human G-CFS is unstable or that any components of their compositions effect stabilization. Nor is there any suggestion that one could combine the references to arrive at a stable glycosylated hG-CFS.

Admitting that Tsuji et al do not claim the weight ratios and pH's of the present invention, the Examiner states that it would have been obvious to one skilled in the art "to determine all operable and optimal weight ratios and pH's for the compositions of the Tsuji et al because weight ratio and pH are art-recognized result-effective variables which are routinely determined and optimized in the pharmaceutical composition arts." The "slight deviations" from Tsuji examples, the Examiner states, do not impart patentability to the claims of the present invention, in the absence of unexpected results.

The applicants respectfully respond that in the present invention, it was unexpectedly found that the pH of the composition is very important to the percent remaining G-CSF after long term storage as well as the low production ratio of desialylated G-CSF after long term storage. This is demonstrated in Figures 1 and 2, and on page 7, lines 5-18. Additionally, the formulation of pH range 6-6.8 provides the most preferable results both in the percentage of remaining G-CSF and the low production ratio of desialylated G-CSF. See page 7, line 7. There is no teaching in Tsuji et al. or any other reference of record that pH is important in this respect. Michaelis et al. merely show that the G-CSF produced in CHO cells in glycosylated.

The Examiner states that the Tsuji et al. "is not limited to any particular weight ratios or pH's." Applicants respectfully reply that this overstates the breadth of the Tsuji et al disclosure. Tsuji et al disclose one weight ratio for each of two non-ionic surfactants and one

pH for both. Without further discussion of the purpose or importance of those ingredients, this meager disclosure cannot be read to include a teaching of any weight ratios and pH's; such a rule would make obvious the proverbial needle in the haystack. The absence of further examples, or disclosure of a range of weight ratios or pH's that overlap the claimed weight ratios or pH's cannot render the narrow claimed weight ratios and pH's obvious. Again, the description on page 7, lines 5-18, and Figures 1 and 2 of the specification demonstrate the importance of pH on the stability of G-CSF composition of the present invention.

Even if the Examiner were correct that adjusting pH or weight ratios was "routine," the person of ordinary skill in the art would first have had to arrive at the claimed combination of ingredients, knowing that ingredients normally added to stabilize such compositions were not necessary to stabilize the composition at the more convenient and cost-efficient storage temperature of 25°C. Only then might that person of ordinary skill in the art have embarked on "routine" adjustments. And even assuming the Examiner is correct that one skilled in the art would have found it "desirable to be able to prepare and store for use all known pharmaceutically active agents," the Examiner does not explain how one skilled in the art would be led away from standard practice of adding stabilizing ingredients such as mannitol and/or proteins, as disclosed in the cited references, and towards the present invention of using a pH below 7 combined with a low ratio (i.e., 1 or less) of surfactant:hG-CSF. That would have required the hindsight of knowing the benefits of the present invention.

Claims 1-5, 7, 8, and 10-12. Examiner has rejected claims 1-5, 7, 8, 10-12 as obvious over Japanese patent application 4-77436 ('436). Applicants respectfully traverse this rejection, finding the disclosure of the '436 application cumulative at best over Tsuji et

al. and Michaelis et al. As with the Tsuji et al. in view of Michaelis et al rejection, the Examiner has not explained how the '436 application would have led, or suggested to, one skilled in the art to choose the compositions claimed in the present application, other than through hindsight, to effect a stable human G-CFS protein formulation.

Japanese application '436 relates to a method of treating cancer using a "cancer metastasis inhibitor." The active ingredient in the '436 application is stated to comprise hG-CSF. The '436 application discloses human G-CSF prepared for medicinal use in humans, by manufacturing with "necessary carriers and excipients" and if needed stabilizer and adsorption preventing agent, etc. '436 at pp. 4-5. The '436 application is silent as to the stability of the composition, other than its storage instructions. The examiner states that the '436 application, like Tsuji et al, "is not limited to any particular weight ratios or pH's." This overstates the breadth of the '436 disclosure for the same reasons recited above for Tsuji et al. This generic disclosure of composition should not be read to include the specific, narrow claimed composition of the present invention. Applicants repeat that pH range of 6-6.8 was unexpectedly found to be very important in both the percentage of remaining G-CSF and the low production of desialylated G-CSF after long term storage, as described on page 7, lines 5-18 and Figures 1 and 2.

Results of the Present Invention are Unexpected

The claims of the present invention are not obvious over Tsuji et al and Michaelis et al or the Japanese application '436 because the results are unexpected. The applicants have surprisingly found, that purified or recombinant hG-CSF may be made stable for storage by formulating a composition having a pH of 6-6.8 and weight ratios of surfactant:hG-CSF of 1 or less. The unexpectedness of these results may be seen in the art cited by the Examiner, Tsuji et al and Japanese application '436. The preparations of Tsuji et al and '436 are

identical in composition and methods of storage. Both references suggest the addition of "stabilizers" if needed. One skilled in the art would recognize the disclosed mannitol and proteins as components to be adjusted for stabilization purposes. Moreover, in both Tsuji et al. and the '436 application, the liquid samples, which did not contain added proteins or mannitol, were stored in the dark at less than 10°C. This disclosure suggests that in the absence of mannitol or protein stabilizers, the preparations were not expected to be stable at room temperature or above for extended storage. Even if the liquid preparations of Tsuji et al. or the '436 application would have been inherently stable at or above 25°C, the stability would not have inevitably occurred, been demonstrated or observed, because the samples were stored in the dark under refrigeration, and were taught to be so stored. For storage at or above 25°C, both Tsuji et al. and the '436 application clearly contemplated lyophilized preparations, containing the stabilizers mannitol and a protein (specifically human serum albumin – Example 3/Practical Example 3, or gelatin – Example 4/Practical Example 4).

By contrast, the applicants have surprisingly found that purified or recombinant glycosylated hG-CSF may be made stable at or above 25°C using a pH of 7 or less and weight ratios of surfactant:hG-CSF of 1 or less, without the need for stabilizing proteins such as albumin or stabilizers such as mannitol. Thus, the results of the present invention are unexpected over the prior art.

CONCLUSION

The currently pending claims, as amended, are neither anticipated by nor obvious over the references of record. Applicants believe the claims are now in condition of allowance and respectfully request that pending claims be allowed.

AUTHORIZATIONS

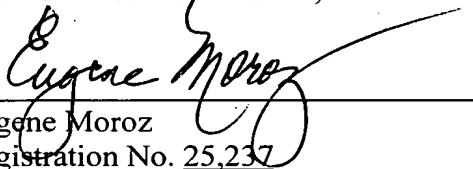
Pursuant to 37 C.F.R. §§ 1.136(a) and 1.17(a), a petition for a three-month extension of time, up to and including November 25, 2002, is submitted herewith, along with the fee for a three-month extension of time.

The Commissioner is hereby authorized to charge any additional fees which may be required for timely consideration of this Amendment under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account No. 13-4500, Order No. 0263-4047.

Respectfully submitted,
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Dated: November 25, 2002

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APPENDIX A

1. (twice amended) A stable granulocyte colony-stimulating factor-containing formulation comprising a granulocyte colony stimulating factor having a sugar chain and at least one pharmaceutically acceptable non-ionic surfactant in [and] an amount of 1 part by weight or less per part by weight of the granulocyte colony-stimulating factor and having a pH of [5-7] 6-6.8, said formulation being substantially free from protein as a stabilizer.
2. The granulocyte colony-stimulating factor-containing formulation of Claim 1 wherein the surfactant is contained in an amount ranging from 0.2 to 1 parts by weight per part by weight of the granulocyte colony-stimulating factor.
3. The granulocyte colony-stimulating factor-containing formulation of Claim 2 wherein the surfactant is contained in an amount ranging from 0.2 to 0.8 parts by weight per part by weight of the granulocyte colony-stimulating factor.
4. The granulocyte colony-stimulating factor-containing formulation of Claim 2 wherein the surfactant is contained in an amount ranging from 0.4 to 0.8 parts by weight per part by weight of the granulocyte colony-stimulating factor.
5. The granulocyte colony-stimulating factor-containing formulation of Claim 2 wherein the surfactant is contained in an amount of 0.4 or 0.8 parts by weight per part by weight of the granulocyte colony-stimulating factor.
7. The granulocyte colony-stimulating factor-containing formulation of Claim 1 wherein the surfactant is at least one non-ionic surfactant selected from the group consisting of sorbitan fatty acid esters, glycerin fatty acid esters, polyglycerin fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene sorbitol fatty acid esters, polyoxyethylene glycerin fatty acid esters, polyethylene glycol fatty acid esters, polyoxyethylene alkyl ethers, polyoxyethylene polyoxypropylene alkyl ethers, polyoxyethylene alkyl phenyl ethers, polyoxyethylene hardened castor oils, polyoxyethylene beeswax derivatives, polyoxyethylene lanolin derivatives, and polyoxyethylene fatty acid amides.
8. The granulocyte colony-stimulating factor-containing formulation of Claim 1 wherein the surfactant is a polyoxyethylene sorbitan fatty acid ester selected from the group consisting of Polysorbate 20 and Polysorbate 80.

10. (canceled) [The granulocyte colony-stimulating factor-containing formulation of Claim 1, which has a pH of 6-6.8.]

11. The granulocyte colony-stimulating factor-containing formulation of Claim 1, which has a pH of 6.2-6.8.

12. The granulocyte colony-stimulating factor-containing formulation of Claim 1, which is packed in a vial, ampoule or prefilled syringe.